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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☐ Claims 1-41 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-24, 28, 29 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 25-27, 30-41 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

35 U.S.C. §101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 25-27 and 30-38, and 41 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The protein growth factor as claimed has the same characteristics and utility as the protein growth factor found naturally and therefore does not constitute patentable subject matter. The phrase "substantially pure" does not properly set forth the intended purity of the growth factor apart from its naturally occurring admixtures. The tests set forth by the court are "A nonnaturally occurring manufacture or composition of matter -- a product of human ingenuity -- having a distinctive name, character, and use." is patentable subject matter. In the absence of the hand of man, the naturally occurring protein growth factor is considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Mere purity of a naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui, 156 USPQ 426 (1966). However, when purity results in a new utility, patentability is considered. Merck Co. v. Chase Chemical Co., 273F. Supp. 68 (1967). See also American Wood v. Fiber Disintegrating Co., 90 U.S. 566 (1974); American Fruit Growers v. Brogdex Co., 283 U.S. 1 (1931); Funk Brothers Seed C. v. Kalo Innoculant Co., 33 U.S.

127 (1948). To overcome this rejection, the Examiner suggests the amendment of the claims to include purity limitations which would distinguish the utility of applicant's product as enabled in the specification from the utility of the source containing the product in nature. It is further suggested that such limitation include the terminology "purified and isolated" and/or a description of what applicant's product is "free of " relative to its utility as distinguished from that of the natural source.

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. §112, first paragraph and claims 39-40 are rejected under 35 USC 112, first paragraph and 35 USC 101 as the specification fails to adequately teach how to use the claimed pharmaceutical composition and the claimed invention lacks patentable utility. The specification does not support the asserted utility of the claimed pharmaceutical composition in vivo. The specification alleges utility of the claimed protein growth factor as an active ingredient in a pharmaceutical composition, however no working examples are set forth which demonstrate in vivo utility. The

claims are based on pure speculation that the composition would be effective in vivo. The success of the claimed composition is dependent on adequate concentrations of drug reaching the desired site in vivo. There are many pharmacokinetic properties of drugs such as half-life, deactivation by the liver, binding to plasma proteins, rapid excretion, etc. that would need to be determined and set forth to establish in vivo utility. No guidelines are presented in the specification which would aid one of skill in the art in selecting parameters for successful use of the pharmaceutical composition.

Claims 30-40 are rejected under 35 U.S.C. §101 as lacking utility, or under 35 U.S.C. 112, first paragraph as failing to enable any person skilled in the art to which it pertains to make and use the claimed products. See MPEP 608.01(p). Applicant is claiming a series of fragments of the protein claimed in claim 25, with various substitutions within the fragmented sequence. These fragments are not set forth in the specification, and therefore there is no description of how to make each fragment or how to use each fragment. The methods of making the substitutions at the designated locations is never described. The fragments are never tested for activity. Furthermore, it cannot be expected that each fragment (and many are encompassed by the broad claim language) would have mitogenic activity. The amino acids being substituted are cysteines, which are often

involved in important secondary structure and proper folding of proteins. Therefore, it cannot be asserted, that without proper tests, or demonstration that these substitutions and deletions can be made without adversely effecting activity, that these proteins would still retain mitogenic activity, i.e. remain useful.

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to the A-chain of PDGF depicted in the figure 1 or 2. Claims 25-27 recite "..or analog of said sequence that is substantially homologous and functionally equivalent thereto" which is overly broad since many proteins could have meet this definition, and be entirely different proteins in structure but are not disclosed. The specification defines "substantially homologous" as less that 10 amino acid substitutions or deletions, however no guidance is provided as to where within the protein these substitutions and deletions can be made. In every protein, there are amino acids that are critical for biological function, proper folding, proper receptor binding, proper internal structure. It is highly unlikely that <u>any</u> amino acid within the PDGF A-chain protein could be substituted or deleted without some alteration of one or more of these functions. Since there is no guidance as to which amino acids are required for these functions, or which areas of the protein are critical, it would require undue experimentation

by one of skill in the art to make or isolate any of the mutant proteins set forth in the claims.

Claims 25-27, and 30-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25-27 are confusing in the recitation of "recombinant". Applicants have defined the term on page 4-5 as "intends DNA of genomic, cDNA, semisynthetic, or synthetic origin...". This is confusing since in the instant claims, "recombinant" is defining a protein, not DNA. If the intent is to define the process by which the protein is made (to possibly distinguish it from the natural protein), the claim then becomes written in a product by process form. The invention defined in a product-by-process claim is a product, not a process. In re Bridgeford, 357 F2d 679, 149 U.S.P.Q. 55 (CCPA 1966). It is patentability of the product claimed and NOT of the recited process steps which must be established. In re Brown, 459 F2d 531, 173 U.S.P.Q. 685 (CCPA 1972); In re Wertheim, 541 F2d, 191 U.S.P.Q. (CCPA 1976). A comparison of the recited process with the prior art processes does NOT serve to resolve the issue concerning the patentability of the product. In re Fessman, 489 F2d 742, 180 U.S.P.Q. 324 (CCPA 1974). Whether a product is patentable depends on whether it is known in the art or it is obvious , and is not governed by whether the process by

which it is made is patentable. In re Klug, 333 F2d 905, 142 U.S.P.Q. 161 (CCPA 1964).

Claims 30-41 are indefinite in the recitation of the term "substantially". "Substantially" is a broad term (see In re Nehrenberg CCPA 126 USPQ 383), and does not set forth the purity of the protein.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that

> the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 25-27, 30-36, and 41 are rejected under 35 U.S.C. § 102(a) as being anticipated by Betsholtz et al.. Betsholtz et al. teaches the amino acid sequence of the PDGF A-chain (see figure 1).

Claims 25-27 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Murray, pn 4889919. Murray claims the exact protein as applicants (see claims 1-12). Also, instant claims 25-27 are anticipated since they are broadly written so as to encompass A-chain homodimers.

Claims 25-27, 30-38, and 41 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Heldin et al., Johnsson et al. (BBRC 1982), or Antoniades et al.. Each of the references teaches the purification and characterization of PDGF, both the A and B chains (see figures 3 and 4 of Heldin et al., figure 4 of Johnsson et al., and figure 1 of Antoniades et al.. The references do not disclose the amino acid sequence of the PDGF A

or B chains, however in view of their similar function, molecular weight, and source, the growth factor disclosed by the references and the growth factor claimed by applicant appear to be the same species. Since the species appear to be identical, the distinguishing features, such as amino acid sequence, would be inherently present in the species disclosed by the references even though these features are not specifically taught.

This rejection is being made under 35 USC 102 and 103 because it is impossible for the Examiner in charge of this application to physically compare the claimed protein and the protein of the prior art. Applicant bears the burden of providing evidence which distinguishes the claimed protein from that disclosed by the references. A preferred means of providing this evidence is for applicant to submit a declaration evidencing a side by side comparison of the protein of the prior art and the claimed protein, which demonstrates material differences and shows the proteins to be distinct and unobvious in view of each other.

Claims 39 and 40 are rejected under 35 U.S.C. § 103 as being unpatentable over Betsholtz et al., Heldin et al., Johnsson et al., or Antoniades et al.. The teachings of the references are recited in the above rejections. The references do not disclose PDGF as a part of a composition with a carrier or diluent, or an adjuvant. However the main ingredient in the composition is the

claimed PDGF protein. Merely adding one or more excipients is an obvious modification, and does not render the claims patentable. One of ordinary skill in the art would be motivated to formulate such a composition since it is known in the prior art that the growth factor may have wound healing properties. Therefore the growth factor composition still reads on the growth factor disclosed by the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shelly Guest whose telephone number is (703) 308-4310. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 308-4227.**

MARGARET MOSKOWITZ
SUPERVISORY
PATENT EXAMINER
ART UNIT 186

sjg
June 5, 1991